UNITED STATES DEPARTMENT OF COMMERCE
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MV

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/160,067 | 09/24/98 | GUNZBURG W | GSF98-04A |

HM12/0118

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| **ART UNIT** | **PAPER NUMBER** |
| 1652 | 10 |

**DATE MAILED:** 01/18/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applic(s) |
|---|---|
| 09/160,067 | Gunzburg et al. |
| **Examiner** | **Group Art Unit** |
| Richard Hutson | 1652 |

☒ Responsive to communication(s) filed on *Nov 18, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claim**

☒ Claim(s) *1-20* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6 & 9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

### *Election/Restriction*

Applicant's election without traverse of group I in Paper No. 8 is acknowledged, although the restriction requirement made in paper No: 7 is hereby withdrawn.

Newly submitted claims 15-20 directed to a pharmaceutical kit comprising the capsule of claim 1 will be examined will be examined with claims 1-14. Therefore, claims 1-20 are examined in this action.

### *Priority*

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark on 3/27/96. It is noted, however, that applicant has not filed a certified copy and a translation of the DK 0352/96 application as required by 35 U.S.C. 119(b).

### *Claim Objections*

Claim 6 objected to because of the following informalities: Claim 6 depends from a rejected claim. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10-12, 16, 17 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite in recitation of "relevant disease or disorder". The application teaches a method for treating a tumor, but fails to define the limitation of those diseases or disorders, such as other cancers or opportunistic diseases associated with cancer, that are also encompassed by "relevant disease or disorder".

Claims 12 and 17 are indefinite in that they are confusing in their recitation of the phrase "and/or" multiple times within each claim.

Claim 16 is indefinite in recitation of "wherein the capsules and the prodrug are formulated in different forms". This claim is unclear as to what are "different forms".

Claims 10 and 20 provide for the use of a capsule according to claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 10 and 20 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for

example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The rejection of claim 10 could be overcome by amendment such as "A method of ablation of a tumor, comprising the direct insertion into said tumor of a cellulose sulphate and polydimethyldiallylammonium capsule, wherein said capsule comprises cells transformed with a DNA sequence encoding cytochrome P450 operably linked to a promoter, wherein expression of said DNA sequence in the presence of a prodrug causes a reduction in tumor size."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cellulose sulphate and polydimethyldiallylammonium capsule encapsulating cells transformed with a DNA sequence encoding cytochrome P450 operably linked to a promoter, wherein said cells express said DNA sequence, does not reasonably provide enablement for any capsule encapsulating any cytochrome P450 producing cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is sufficiently broad as to encompass any capsule encapsulating any cytochrome P450 producing cell. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of capsules encapsulating

cytochrome P450 producing cells broadly encompassed by the claims. Since the material used to synthesize the capsule determines its structural and functional properties, predictability of which material can be used to synthesize the capsule to produce the desired properties, requires a knowledge of how the encapsulation material relates to its functional properties. As the claims require that the prodrug pass into the capsule, the pore size needs to be of proper size to permit such. The only guidance provided by the specification is a capsule produced by cellulose sulphate and polydimethyldiallylammonium. Given a lack of discussion of any materials that would produce a proper pore size, the claims are only enabled for a capsule made of cellulose sulphate and polydimethyldiallylammonium.

Since the cell used to synthesize cytochrome P450 determines the level of cytochrome P450 produced, predictability of which cells can be used to synthesize sufficient cytochrome P450 to affect tumors, requires a knowledge or teaching of how the level of expression of cytochrome P450 produced by the cell relates to the desired use. The instant specification provides no guidance as to those cells that naturally produce cytochrome P450 in situ which would when encapsulated produce sufficient cytochrome P450 to cause an affect on a tumor or cancer.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any capsule encapsulating any cytochrome P450 producing cell. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re

Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those capsules comprising cytochrome P450 producing cells having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 11-15 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing a tumor comprising the direct insertion of the capsule into the tumor wherein expression of the DNA sequence results in an inhibition in tumor growth or a decrease in tumor size, does not reasonably provide enablement for a method of treating a cancer disease or any other relevant disease or disorder comprising administering to a subject in need thereof a therapeutically effective amount of the capsule of claim 1 and, either simultaneously or with a time span, a prodrug which is activated by cytochrome P450. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 11 is sufficiently broad as to encompass any method of treating a cancer disease or any other relevant disease or disorder comprising administering to a subject in need thereof a therapeutically effective amount of the capsule of claim 1 and, either simultaneously or with a time span, a prodrug which is activated by cytochrome P450. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large

number of diseases or disorders and methods of administering said capsule broadly encompassed by the claims. Since a method of treating any relevant disease or disorder, requires a knowledge of the physiological basis of said disease or disorder and its relationship to cytochrome P450 and the co-administered prodrug, those diseases encompassed by the claim are unpredictable and methods of their treatment would require undue experimentation by one of ordinary skill in the art. Relevant diseases or disorders may encompass other types of cancer such as leukemia and other associated disorders such as opportunistic pneumonia. At no place does the specification discuss methods of treatment of these relevant diseases or disorders. The specification only teaches a method of decreasing a tumor comprising the direct insertion of the capsule into the tumor wherein expression of the DNA sequence results in an inhibition in tumor growth or a decrease in tumor size.

Additionally, the route of administration of said capsule encapsulating a cytochrome P450 producing cell effects the success of any method of treating a disease, and thus predictability of those routes of administration of said capsule which would result in successful treatment of said disease, encompassed by the claim are unpredictable and would require undue experimentation to one of ordinary skill in the art. The guidance in the specification as seen in example 10, only provides guidance for the direct insertion of capsules encapsulating cytochrome P450 producing cells into tumors. There is no guidance for other results of administration. In particular there is no evidence that by systemic administration sufficient capsules would reach the target tumor to

have any affect on the tumor. At no place does the specification discuss methods of "homing" the encapsulated cells to a particular tumor, organ or tissue.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any capsule encapsulating any cytochrome P450 producing cell. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those relevant diseases or disorders as well as method of administering said capsule is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5, 7-20 rejected under 35 U.S.C. 102(a) as being anticipated by Saller et al. (WO 97/01357).

Saller et al. teach the use of encapsulated cells producing viral particles for the treatment of tumors. Saller et al. specifically teach capsules formed from cellulose sulphate and polydimethyldiallyl-ammonium comprising a packaging cell containing a replication defective retroviral construct carrying the cytochrome P450 gene, pLX125 (Example 4). Saller et al. also teach a pharmaceutical composition comprising said capsule and its use for the treatment of cancer (page 11). Saller et al. further teach use of the above capsule in combination with a prodrug for the treatment of tumors (page 11).

Therefore, claims 1-5, 7-20 are anticipated by Saller et al.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8, 9,15, 16, 17, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al. (Human Gene Therapy 5: 969-978, 1994) and Tai et al (FASEB Journal 7: 1061-1069, 1993).

Wei et al. teach that malignant tumors of the central nervous system do not respond well to chemotherapy, specifically cyclophosphamide (CPA) because the conversion of CPA to DNA-alkylating cytotoxic metabolites is restricted to the liver. Wei et al. further teach that cytochrome

P450 2B1 activates the inert prodrug, CPA into its cytotoxic metabolites. Wei et al. further teach that the addition of cytochrome P450 2B1-producing fibroblasts followed by CPA administration, prevented meningeal neoplasia and led to partial regression of parenchymal solid tumors in the brains of athymic mice, previously seeded with rat C6 gliomas.

Tai et al. teach an alternate strategy of gene therapy that involves immunoisolating genetically modified cells in a biocompatible membrane (a capsule), thereby introducing a system that can provide sustained delivery of the desired gene product to a tissue or group of cells. The microencapsulation delivery method of Tai et al. overcomes problems associated with somatic gene therapy such as the inability to achieve efficient gene transfers, obtaining sustained level of expression of the transfected gene and the necessity to avoid immunorejection after transplantation. Tai et al. used an alginate -poly-L-lysine semipermeable membrane that provided a microenviroment that was physiologically compatible with the growth of the modified cells and allowed easy diffusion of the secreted gene products without compromising the immunoisolating properties of the membrane.

One of ordinary skill in the art at the time of filing would have been motivated to encapsulate the cytochrome P450 2B1-producing fibroblasts of Wei et al. in the capsule of Tai et al. such that said capsule comprises a porous membrane that allows cytochrome P450 to pass out of the capsule as well as the prodrug molecule, CPA, to pass into the capsule in order to supply cytochrome P450 activity to the prodrug, CPA, for its use as a chemotherapeutic agent. The ordinary artisan at the time of filing would have been further motivated to microencapsulate the

cytochrome P450 2B1-producing fibroblasts of Wei et al. in the capsule of Tai et al. in order to overcomes problems associated with somatic gene therapy such as the inability to achieve efficient gene transfers, obtaining sustained level of expression of the transfected gene and the necessity to avoid immunorejection after transplantation as discussed above by Tai et al.

The ordinary artisan would have had a reasonable expectation of success at the time of filing based on the results of Wei et al. who showed that the addition by inoculation of cytochrome P450 2B1-producing fibroblasts to mice brains followed by CPA administration prevented meningeal neoplasia as well as the results of Tai et al. that showed significantly higher levels of human growth hormone from the recipients of encapsulated cells relative to the recipients of unencapsulated cells.

Further the ordinary artisan would have been motivated at the time of filing to use the above capsule as part of a pharmaceutical composition or kit for the treatment of a cancer, because of the shown effectiveness of cytochrome P450 producing fibroblasts in helping to reduce tumor growth when administered in conjunction with the appropriate prodrug as taught by Wei et al. The ordinary artisan would have been motivated at the time of filing to also include in said pharmaceutical kit, the prodrug which is activated by cytochrome P450, in a different form because by supplying both components together as a kit, it makes their intended use easier. Wei et al., administered the prodrug cyclophosphamide in combination with the cytochrome P450 2B1-producing fibroblasts as a treatment for inhibiting tumors.

Therefore, claims 1, 8, 9, 15, 16, 17, 18 and 19 are made obvious by Wei et al. and Tai et al.

Claim 2 rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al. and Tai et al. as applied to claim 1, 8, 9, 15, 16, 17, 18 and 19 above, and further in view of Merten et al. (Cytotechnology 7(2): Abstract , 1991).

Merten et al. teach a method for encapsulation of mammalian cells using capsules comprising cellulose sulphate and poly-dimethyl-diallyl-ammonium chloride (PDMDAAC).

One of ordinary skill in the art would have been motivated at the time of filing, to encapsulate, as taught by Tai et al., the cytochrome P450 2B1-producing fibroblasts of Wei et al., in a capsule made of cellulose sulphate and poly-dimethyl-diallyl-ammonium chloride as taught by Merten et al. because of advantages of encapsulating by this method compared to other methods due to the simplicity of the process.

Therefore, Wei et al., Tai et al. and Merten et al. make obvious claim 2.

Claims 4, 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al. and Tai et al. as applied to claims 1, 8, 9, 15, 16, 17, 18 and 19 above, and further in view of Salmons et al. (Leukemia 9 (Suppl. 1): S53-S60, 1995).

Salmons et al. teach the use of retroviral vectors (RV) for gene therapy and discuss the advantages and disadvantages of there use. They teach the construction of retroviral vectors (RV) for targeted delivery and expression of therapeutic genes for gene therapies aimed at treating various cancers, inherited disorders and viral infections. They further teach that

retroviral vectors are the vector of choice for gene transfer because the biology of the retrovirus is relatively well understood, the vector systems give relatively high titres of recombinant virus and because of the availability of retroviral variants which efficiently infect human cells. Salmons et al. teach that because of size constraints in terms of the maximum length of RNA that can be packaged and the necessity to replace the retroviral coding information with the gene product to be produced, retroviral vectors are by definition replication defective (Figure 2). Salmons et al. teach that engineered packaging cell lines give rise to transcripts that direct the synthesis of authentic viral Gag, Pol, and Env proteins, yet lack the necessary signal for the packaging of RNA into virion particles. Upon transfection of a RV construct containing the therapeutic gene into the packaging cell, the resultant vector RNA is packaged by the retroviral proteins and the recombinant virus is released. After infection of a target cell, the recombinant retroviral vector RNA is reverse transcribed, integrated into the host cell DNA and the therapeutic genes expressed. In the absence of the genes encoding the Gag, Pol and Env proteins, further virus cannot be expressed, thus the retroviral vector is replication defective. Salmons et al. further teach that an in vivo approach to the use of retroviral vectors involves the implantation of a virus producing cell, the packaging cell. Salmons et al. teach that these retroviral vectors should be replication defective so as not to lead to insertional activation of cellular proto-oncogenes or inactivation of tumor suppressor genes resulting in tumor formation.

One of ordinary skill in the art would have been motivated at the time of filing, to encapsulate, as taught by Tai et al., a cytochrome P450 producing cell as taught by Wei et al. and

discussed above, wherein the cell is a packaging cell comprising a replication defective retroviral vector as taught by Salmons et al. carrying the cytochrome P450 gene in order to produce infective cytochrome P450 encoding retroviral vector capable of infecting a target tumor cell while the packaging cell remains immunoisolated. One of ordinary skill would have been motivated to place the above retroviral vector encoded cytochrome P450 gene under control of a target cell specific regulatory element or promoter so that the cytochrome P450 gene product would only be produced in the desired target cell, and not another cell where its production could be detrimental to the cell.

One of ordinary skill would have had a reasonable expectation of success at the time of filing based on the results of Wei et al. who showed that the addition by inoculation of cytochrome P450 2B1-producing fibroblasts to mice brains followed by CPA administration prevented meningeal neoplasia as well as the results of Tai et al. that showed significantly higher levels of human growth hormone from the recipients of encapsulated cells relative to the recipients of unencapsulated cells as well as Salmons et al. who show successful results using the retroviral vector system for the expression of exogenous genes (Figure 4).

Therefore, claims 4, 5 and 7 are made obvious over Wei et al. and Tai et al. in view of Salmons et al. (Leukemia 9 (Suppl. 1): S53-S60, 1995).

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al., Tai et al. and Salmons et al. as applied to claim 4, 5 and 7 above, and further in view of Gunzburg et al. (WO 96/07748A1).

Gunzburg et al. teach a retroviral vector useful as a gene transfer vehicle for targeted gene therapy. Specifically, Gunzburg teaches a retroviral vector comprising a 5' LTR region of the structure U3-R-U5; one or more sequences selected from coding and non-coding sequences; and a 3' LTR region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence, followed by the R and U5 region. The retro viral of Gunzburg et al. is a safe gene transfer vehicle for targeted gene therapy with a reduced probability to undergo recombination with the packaging construct.

As discussed above, one of ordinary skill in the art would have been motivated at the time of filing, to encapsulate, as taught by Tai et al., a cytochrome P450 producing cell as taught by Wei et al. and discussed above, wherein the cell is a packaging cell comprising a replication defective retroviral vector as taught by Salmons et al. carrying the cytochrome P450 gene in order to produce infective cytochrome P450 encoding retroviral vector capable of infecting a target tumor cell while the packaging cell remains immunoisolated. One of ordinary skill in the art would have been further motivated at the time of filing to use the retroviral vector taught by Gunzburg et al. that encodes cytochrome P450 gene as the gene transfer vehicle because of its reduced probability to undergo recombination with the packaging construct, thus resulting in prolonged production of cytochrome P450 encoding retroviral vector.

Therefore claim 6 is made obvious by Wei et al., Tai et al., Salmons et al. and Gunzburg et al.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13 and 15 of copending Application No. 08/996,460. Although the conflicting claims are not identical, they are not patentably distinct from each other because they claim common subject matter, A capsule encapsulating a cytochrome P450 producing cell, said capsule comprising a porous membrane which allows prodrug to pass into the capsule, wherein the cytochrome P450 producing cell is a packaging cell comprising a retroviral vector carrying the cytochrome P450 gene.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on M-F from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy (Murthy), can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Richard Hutson Ph.D.
1/14/00